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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

19900 MacArthur Blvd., Ste 300
Irvine, California 92612-2445
Telephone (714) 798-7600

WARNING LETTER

January 14, 2002

WL–24-02

Philip Ottiger
President and CEO
Bachem California, Inc
3132 Kashiwa Street
Torrance, CA 90505

Dear Mr Ottiger:

During an inspection of your pharmaceutical manufacturing facility conducted from November 13 to 27, 2001, our investigators found significant deviations from the current Good Manuacturing Practice (cGMP) for Finished Pharmaceuticals Regulations (Title 21, Code of Federal Regulations (CFR), Parts 210 and 211). These deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act) as follows:

1. Failure to ensure that cleaning methods used in cleaning production equipment will sufficiently prevent contamination that would alter the safety, identity, strength, quality, or purity of drug products [21 CFR 211.67]. Specifically, no documented evidence exists to demonstrate the effectiveness of cleaning methods and agents used in cleaning of all production equipment and utensils to ensure that residues have been reduced to acceptable levels. Cleaning validation is limited to only glassware. Additionally, your firm failed to conduct investigation(s) of out of specification results obtained during the cleaning validation for lyophilization trays. There is no cleaning validation for screens or wire electrodes that have product contact during lyophilization. Our investigators also observed foreign substances on production screens and trays.

2. Failure to establish, implement and control procedures for maintenance, including utensils, used in the manufacture, processing or holding of drug products [21 CFR 211.67]. Specifically, our investigators observed that tape is used to hold your production trays and screens together and tape residues were also observed on the frames of the trays; the frames were also frayed. Our investigators also observed that the wire metal electrodes used for monitoring the temperature of product were frayed. There is no preventative maintenance for the electric wires that are placed in product solutions during tray lyophilization to determine product temperature.

The nitrogen filters in the lyophilizers have not been changed since 1998. The filters are to be changed annually per the labeling instructions on the filter housing. Also, there is no routine maintenance program for these filters. Our investigators determined that a tray lyophilizer was not functional and the equipment maintenance log did not document that status.

3. Failure to ensure that written production and process controls are designed to assure that drug products have the identity, strength, quality and purity they purport or are represented to possess [21 CFR 210.100]. Specifically, no eutectic temperature or sublimation temperatures have been established for any of your drug products. There is no documented evidence to assure that the vacuum and condenser temperatures are maintained throughout your routine manufacturing lyophilization cycle. There is no documented evidence to ensure that the product is completely frozen in an acetone bath with dry ice prior to lyophilization. There is no scientific rationale that assures that in-process lyophilization drying is complete. In addition, no maximum drying time has been established.

4. Failure to ensure that laboratory controls include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity [21 CFR 211.160(b)(1)]. Specifically, there are no requirements for HPLC column system suitability that are applicable to the purification process of your drug products.

5. Failure to ensure that batch production record and control records include complete information relating to the production and control of each batch of drug product [21 CFR 211.188]. Specifically, tray lyophilization charts in batch records are not set up to accurately assess if running parameters are maintained throughout the cycle. Storage conditions for sidecuts are not specified. No tray lyophilization parameters are specified for purification. No yield calculation is performed after purification for each step except for [redacted]

We acknowledge that you have submitted to this office written responses to the form FDA-483. We have reviewed your responses and while these responses address several of our concerns, there still remain several issues that could not be completely evaluated because the supporting documentation was not submitted with those responses, or the responses were inadequate. Detail comments are listed on Attachment A to this letter.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. A list of observations (FDA-483) was issued and discussed with you at the conclusion of the inspection. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice regulations and other applicable regulations. Federal agencies are advised of the issuance of all warning letters

about drugs and devices so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to do so may result in regulatory action without further notice, including seizure and/or injunction. You should notify this office in writing, within fifteen (15) working days of receipt of this letter, of the specific steps you have taken to correct the noted violation, including an explanation of each step taken to prevent the recurrence of similar violations. If corrective action can not be completed within (15) working days, state the reason for the delay and time within which the corrections will be completed.

Your reply should be addressed to:

Thomas Sawyer, Director of Compliance
U.S. Food and Drug Administration
19900 MacArthur Blvd., Suite. 300
Irvine, CA 92612

Sincerely,

Alonza E. Cruse
District Director

Enclosure: Attachment A, Comments on responses to form FDA-483 observations.

Cc: State Department of Public Health
Environmental Health Service
Attn: Chief Food and Drug Branch
601 North 7th Street MS-357
P.O. Box 942732
Sacramento, CA 94234

Bachem California, Inc. W.L

ATTACHMENT A

Your response to form FDA 483 observation 3 does not include a determination of toxicity. When grouping similar products and using worst case scenarios the products should be similar in mode of administration and worst case. Factors to be considered in setting limits should include potency, toxicity, allergenicity, size of subsequent product batch, daily intake of subsequent product (dosage), shared equipment surface area, safety factors, assay sensitivity and cleaning process capability level of visual detection. Additionally, your targeted completion date of end of 2002 for completing your evaluations of your equipment cleaning process is not justified.

Your response to form FDA 483 observation 6 does not include any timeframes for achieving corrective action and that tape will continued to be used to hold the screens and trays together. This is unacceptable in a manufacturing area where product contact is inevitable.

Your response to form FDA 483 observation 7 does not specify that the plastic or rubber lining protecting the electrical wires will no longer be cut down to expose additional wiring, thus making the plastic/rubber frayed and unacceptable for product contact.

Your responses to form FDA 483 observation 18 indicates that to assure that the product temperature gradient remains below the phase diagram temperatures at all concentrations throughout the sublimation, a visual inspection of the resulting cake must be performed. Your response does not indicate that this inspection is documented.